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CITIZEN PETITION

The undersigned, on behalf of Novartis Pharmaceutical Corporation ("Novartis"), submits this petition pursuant to Section 505(e) of the Food, Drug and Cosmetic Act, 21 U.S.C. § 355(e) (the "Act"), and 21 C.F.R. § 10.30 to request that the Secretary of Food and Drugs withdraw approval for the pharmaceutical formulation URSO®, which is the proprietary name for ursodeoxycholic acid (ursodiol), indicated for the treatment of biliary cirrhosis in humans, unless the name of the product is changed. Novartis is initiating this administrative proceeding because of a recent survey which shows that the short name "urso" is commonly used by physicians as shorthand when referring to generic ursodiol products. As discussed more fully below, such usage poses an imminent hazard to the public health since "urso" has long been associated with the ursodiol prescription drug marketed under the name ACTIGALL®. Unlike URSO ursodiol, ACTIGALL ursodiol products are indicated for use in the treatment of gallbladder stones. Further, the recommended dosage for ACTIGALL ursodiol is different than the recommended dosage for URSO ursodiol products. According to the survey, since the term "urso" is commonly used as shorthand for ursodiol products and ACTIGALL is often called "urso", interchange between URSO ursodiol products and ACTIGALL ursodiol products could cause significant medication errors due to their different recommended dosages and indications. Furthermore, even the manufacturer of URSO has freely admitted (as set forth in more detail below) that the proprietary name URSO for its own product has caused substitution errors.

ACTIONS REQUESTED

Novartis requests that the Food and Drug Administration ("FDA" or "Agency") withdraw approval of the abbreviated NDA application for URSO unless the name of the product is changed. In addition, Novartis requests that should any applicant pursue approval of an ursodiol product in the future, the FDA at a minimum require the clearance of a name which does not incorporate or suggest the term "urso".

STATEMENT OF GROUNDS

Introduction

Ursodiol is a naturally occurring bile acid found in small quantities in normal human bile and in larger quantities in the bile of certain species of bears. It is a bitter tasting white powder freely soluble in ethanol, methanol, and glacial acetic acid; sparingly soluble in chloroform; slightly soluble in ether; and practically insoluble in water.

Ursodiol suppresses hepatic synthesis, secretion of cholesterol and absorption of cholesterol. With repeated dosing, ursodiol concentrations in the bile reach steady state levels in three weeks. There, it is capable of solubilizing and dispersing cholesterol crystals. The various actions of ursodiol combine to change the bile of patients with gallstones from cholesterol precipitating to cholesterol solubilizing, thus resulting in bile conducive to cholesterol stone dissolution. As such, ursodiol is indicated for the treatment of radiolucent, noncalcified gallbladder stones and for the prevention of gallbladder stones in obese patients experiencing rapid weight loss.

It is also suspected that long-term treatment with ursodiol might displace endogenous bile acids from the enterohepatic circulation and thus reverse their suspected toxicity. As such, ursodiol is indicated for the treatment of primary biliary cirrhosis ("PBC").

DEVELOPMENT OF ACTIGALL® AND URSO®

Novartis is a research based pharmaceutical company and is widely acknowledged to be a pioneer in the development of drugs and medicines which preserve and improve the quality of human life. Development of ursodiol began in the mid 1980s. Based upon extensive preclinical testing and clinical studies, Novartis

first secured approval for an ursodiol product in December, 1987. Novartis named its ursodiol product ACTIGALL and launched the brand in November, 1988. ACTIGALL is indicated for the treatment of noncalcified gallstones in humans, particularly individuals with an increased surgical risk due to systemic disease, advanced age, idiosyncratic reaction to general anesthesia, or those patients who refuse surgery.

The recommended dosage for ACTIGALL is 8-10 mg/kg/day which is administered by a 300 mg capsule two to three times daily. Agents such as aluminum based antacids, cholestyramine and colestipol, however, may interfere with ACTIGALL'S metabolism and decrease its effectiveness.

After many years of successful ursodiol use by Novartis for the treatment of gallbladder stones, investigations began into whether ursodiol could be used to treat conditions suspected to be related to bile acid toxicity. Clinical trials soon demonstrated that ursodiol was effective for the treatment of primary biliary cirrhosis. Thereafter, Axcan Pharma U.S., Inc. ("Axcan") submitted a NDA application, pursuant to Section 505(j) of the Act, for approval of ursodiol for the treatment of primary biliary cirrhosis. Axcan chose the name URSO for its ursodiol product. On December 11, 1997, the FDA approved Axcan's application. The recommended dosage of URSO ursodiol for the treatment of primary biliary cirrhosis is 13-15 mg/kg/day which is administered by a 250 mg tablet four times daily.

Survey Evidence For Risk of Medication Errors

Pursuant to Section 505(e) of the Act, 21 U.S.C. § 355(e), the Secretary of the Agency shall withdraw approval of an application with respect to any drug under this section if the Secretary finds that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon which the application was approved. In addition, the Secretary may suspend the approval of an application immediately if the Secretary finds that the drug poses an imminent hazard to the public health.

The term "urso" (the short form of ursodiol), is commonly used by health care professionals to refer to generic ursodiol products and the Novartis ursodiol product ACTIGALL. The prevalence of the short form use is so extensive that a practitioner entering "urso" into the electronic Physicians Desk Reference (PDR), retrieves ACTIGALL as the product. Concerned

that the perception in the marketplace would be that Axcan's URSO carried the same indications as Novartis' ACTIGALL, Novartis commissioned a survey to assess the risk of medication errors by physicians confusing the two products.

The survey, entitled "Ursodeoxycholic Acid (Ursodiol) Survey Report; Is There Confusion Potential Between Urso and Other Ursodiol Products and Could It Lead to A Medication Error?", was prepared and conducted by the independent non-profit organization Med-Errs™, a subsidiary of the Institute for Safe Medication Practices (ISMP). (See Survey attached hereto as Exhibit A)

The results of the survey show that there is strong evidence that confusion between URSO ursodiol products and other ursodiol products will be created as a result of the common usage of the short name "urso" and that such confusion is likely to lead to medication errors. The survey polled gastroenterologists, hepatologists/surgeons and pharmacists.

Significantly, 21% of the gastroenterologists who responded to the survey have written prescriptions for ursodiol using the "urso" short form. For these prescribers, 34% of their prescriptions are written in short form. In addition, 42% of the gastroenterologists indicated that use of the short form "urso" for ursodiol is acceptable in their institution/practice as a substitute name for any ursodiol product. This is an alarming rate given the commonality of verbal prescription orders. A recent article written by Daniel Boring of the FDA and attached hereto as Exhibit B states: "Because verbal requests for pharmaceuticals in hospital and retail settings are common, a new trademark should not sound like existing trademarks, generic terms, medical terms, or medical abbreviations." Daniel Boring, Avoiding Trademark Trouble at FDA, Pharmaceutical Executive, June 1996. The concern here is that URSO not only sounds like "urso," but it is used freely as an alternative term to ursodiol and thus, as supported by the survey results, is likely to result in prescribing errors.

Although the survey did not show that "urso" is an accepted short form in pharmacies for ursodiol, an overwhelming number of pharmacists (94%) capable of re-stocking drugs by computer indicated that ACTIGALL can be ordered simply by entering the short form "urso." 23% of pharmacists indicated that multiple ursodiol products (i.e.: URSO and ACTIGALL) can be ordered using the "urso" short form. In addition, 67% of responding pharmacists reported that they could generate computer

prescription labels by entering the short form "urso" into their systems. Of those, just 16% of the computers will list multiple ursodiol products while the remaining 84% of screens list either URSO, ACTIGALL or ursodiol. Perhaps this is the reason that Axcan has itself noted that the two ursodiol products are indeed substituted for each other at pharmacies. See Exhibit C.

In view of widespread use of the short form "urso" for ACTIGALL, the presence of a dosage strength and frequency on the prescription form appears essential to allow differentiation between an order for URSO and ACTIGALL. Pharmacists reported, however, that as many as 13% of prescriptions written for an ursodiol product omit dosage strengths and 22% omit daily dosage frequency. Considering the serious nature of the indications for URSO and ACTIGALL and different daily dosages for each, the survey found that the possibility of a serious medication error occurring is high.

As Mr. Boring wrote in his article Avoiding Trademark Trouble at FDA, it has been the practice of the FDA and the U.S. Adopted Names Council (USAN) to encourage companies to abandon the practice of using a generic "stem" as the key component of a brand name. He cites as an example fatal medication errors occurring from the use of "platin" (the USAN stem for a class of anti-cancer agents) in Platinol (cisplatin) and Paraplatin (carboplatin). Similar types of errors were also noted in an article written by George DiDomizio. See The New Rules and Realities For Pharmaceutical Trademarks, Trademarks America, May 1993, atached hereto as Exhibit D. Mr. DiDomizio cited errors in which a prescribing physician wrote the unapproved short form "norflox" instead of the brand name Noroxin for the generic antibiotic product norfloxacin. In that case, the retail pharmacist dispensed the muscle relaxant Norflex. The error was only discovered when the patient became weak and suffered from hallucinations. These cases demonstrate that prescribing errors caused by confusion due to the similarity of generic stems are not simply theoretical, but are common and often dangerous occurrences. In the present situation, the generic component URSO is not a key component of a brand name, it is the brand name.

Effect of Medication Errors on Public Health

To the many patients who suffer from gallstones or biliary cirrhosis, the risk of a medication error caused by the erroneous interchange between URSO and ACTIGALL poses an imminent health

hazard. For example, a 160 pound patient with gallbladder stones would typically be prescribed 300 mg of ACTIGALL to be taken twice daily, the total dose being 600 mg per day. As set forth above, if the patient's prescription is written for "urso" (the short form for ursodiol) as the survey indicates is often done, and is mistakenly filled with URSO, the patient will receive 250 mg tablets instead of 300 mg capsules. The result of the error is that the patient only receives 500 mg of ursodiol per day, approximately 17% less than the prescribed amount of 600 mg per day for a patient on a twice-daily dosing regimen. The error is compounded in patients taking antacids whose body levels of ursodiol may already be decreased. This problem is particularly pertinent since heartburn and diarrhea are two of the leading adverse effects associated with ursodiol. Thus it would be expected that many ursodiol users are likely to be taking antacids as well.

According to Dr. Thomas Garvey, an expert gastroenterologist and President of Garvey Associates, Inc., a scientific/medical consulting firm in Potomac, Maryland, a mistake in which URSO is dispensed to a patient instead of ACTIGALL could significantly affect the minimum therapeutic levels of ursodiol necessary to effectively treat gallbladder stones. In his affidavit, attached hereto as Exhibit E, Dr. Garvey explains that "one-for-one substitution of URSO tablets for ACTIGALL capsules would result in substantial underdosing (about 17%) for all regimens [gallbladder stone dissolution and prevention]." As a result, Dr. Garvey estimates that the underdosing of patients receiving ACTIGALL ursodiol would result in a 10% greater risk of gallstone formation in patients on a very low calorie weight loss diet and a 24.4% increase in risk of gallstone accumulation in patients experiencing rapid weight loss as a result of gastric bypass surgery.

Dr. Garvey further explains that many of the patients who develop gallstones as a result of underdosing will become symptomatic, experiencing severe pain and acute cholecystitis. Since surgical laparoscopic cholecystectomy is the most commonly employed treatment for gallstones, Dr. Garvey opines that underdosing arising from substitution of URSO and ACTIGALL is likely to result in serious injury to some patients due to the risk of serious bile duct injury associated with laparoscopic cholecystectomy. Moreover, such surgery is not only expensive but frequently unsuccessful. In view of the foregoing, Dr. Garvey recommends that Axcan Pharma be required to rename their

formulation of ursodiol so that any chance of confusion or substitution between ACTIGALL and URSO is mitigated.

Dr. Garvey's opinion and recommendations are supported by one of the highest volume prescribers of ACTIGALL in the United States. According to Dr. Vivienne Matalon, an expert in internal medicine and bariatrics, it is common practice among healthcare practitioners to refer to ACTIGALL as "urso", the short form of its chemical name ursodioxycholic acid and its common name ursodiol. In her affidavit, attached hereto as Exhibit F, Dr. Matalon indicates that erroneous switching of ACTIGALL ursodiol and URSO ursodiol products is likely to occur due to the common use of the "urso" short name. In Dr. Matalon's opinion, patients prescribed ACTIGALL for prevention of gallbladder stone formation who erroneously receive URSO ursodiol will be receiving sub therapeutic doses of ursodiol since ACTIGALL is available only as 300 mg capsules while URSO is available as 250 mg tablets. In view of the potential for underdosing, Dr. Matalon recommends that the Axcan Pharma's URSO product be renamed to avoid the likelihood of erroneous switching of URSO and ACTIGALL. Dr. Matalon also recommends that subsequent renaming of the URSO brand not include the formative "urso" which is the common name for the chemical entity ursodioxycholic acid.

Both Dr. Garvey and Dr. Matalon agree with the results of the ISMP survey that continued use of the name URSO for ursodiol is likely to cause confusion and lead to medication errors. If the name of the Axcan Pharma product is not changed, they fear that many patients treated with ursodiol for gallbladder stones will be caused to suffer severe disabling pain, stress and immobility as a result of underdosing with URSO.

The concerns of Dr. Garvey and Dr. Matalon are well founded. Prescribing errors and dispensing errors have already occurred, prompting even the manufacturer of URSO ursodiol to warn patients receiving the URSO brand for the treatment of primary billiary cirrhosis of the potential for such mistakes. In a memorandum sent to members of an on-line internet PBC support group, dated September 28, 1998, attached hereto as Exhibit C, Axcan Director of Management, Stephen M. Casey, admits that "[m]any PBC patients have been treated with ACTIGALL and they have been improperly started at 10-12 mg/kg. This error commonly occurs because the

dosing for ACTIGALL is based on its only approved use, the dissolution of gallstones."[1]

Mr. Casey also cautions that some pharmacists are indiscriminately substituting URSO ursodiol and ACTIGALL ursodiol as if both formulations are bioequivalent when in fact URSO is only available as a 250 mg tablet and ACTIGALL is available only as a 300 mg capsule. Mr. Casey states: "[s]ome pharmacists are improperly making the assumption that both ursodiol products are the same. However, the U.S. Food and Drug Administration denied an application for ACTIGALL's effectiveness in PBC. For your information, the pharmacists who are dispensing ACTIGALL when the physician prescribes URSO, are essentially breaking the law if they do not get clearance from you and your physician to make the substitution. URSO is a white tablet with 'UR785' imprinted on it. ACTIGALL is a pink and white capsule with ACTIGALL 300 mg imprinted on it."

While his legal conclusions are questionable, Mr. Casey's memorandum supports the opinions of Dr. Matalon and Dr. Garvey that the threat of medication errors occurring, due to the use of URSO as a brand name for ursodiol, is not only real but has occurred and will continue to occur.

In view of the foregoing evidence, namely, (i)the independent survey by ISMP showing the likelihood of medication errors; (ii) the statements from two well-known expert physicians who dispense ursodiol in their daily practice that erroneous substitution between ACTIGALL and URSO could cause harm to patients; and (iii) the admission by Axcan that erroneous substitution has already occurred, it is clear that the FDA's approval of URSO should be withdrawn pending a change in the product's name.

CONCLUSION

Accordingly, Novartis hereby petitions the FDA to withdraw approval of Axcan's application for the drug URSO, indicated for use in the treatment of primary biliary cirrhosis until the name of Axcan's product is changed to avoid confusion with ursodiol products including ACTIGALL, commonly referred to in the

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[1] It should be noted that this item of direct-to-consumer promotion for URSO contains no fair balance as required by the FD&C Act and the regulation promulgated thereunder.

healthcare field by the short form "urso", and the first market entry for ursodiol. Novartis further requests that should any applicant pursue approval of an ursodiol product in the future, the FDA at a minimum require the clearance of a name which does not incorporate or suggest the term "urso".

C. ENVIRONMENTAL IMPACT

The actions requested herein qualify for categorical exclusion from the requirement of issuance of an environmental impact assessment pursuant to 21 C.F.R. § 25.24 (a)(c). In any case, Novartis does not believe that any substantial environmental impact will result from the relief requested.

D. ECONOMIC IMPACT

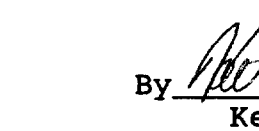
Novartis will provide data concerning the potential economic impact of the relief requested should such information be requested by the Commissioner pursuant to 21 C.F.R. § 10.30(b).

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and includes representative data and information known to Novartis which are unfavorable to the petition.

Respectfully submitted,

NIMS, HOWES, COLLISON,
HANSEN & LACKERT

By 
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